

Toxicant-induced Loss of Tolerance—An Emerging Theory of Disease?

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This paper attempts to clarify the nature of chemical sensitivity by proposing a theory of disease that unites the disparate clinical observations associated with the condition. Sensitivity to chemicals appears to be the consequence of a two-step process: loss of tolerance in susceptible persons following exposure to various toxicants, and subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations including caffeine and alcohol. Although chemical sensitivity may be the consequence of this process, a term that may more clearly describe the observed process is *toxicant-induced loss of tolerance*. Features of this yet-to-be-proven mechanism or theory of disease that affect the design of human exposure studies include the stimulatory and withdrawal-like nature (resembling addiction) of symptoms reported by patients and masking. Masking, which may blunt or eliminate responses to chemical challenges, appears to have several components: apposition, which is the overlapping of the effects of closely timed exposures, acclimatization or habituation, and addiction. A number of human challenge studies in this area have concluded that there is no physiological basis for chemical sensitivity. However, these studies have failed to address the role of masking. To ensure reliable and reproducible responses to challenges, future studies in which subjects are evaluated in an environmental medical unit, a hospital-based facility in which background chemical exposures are reduced to the lowest levels practicable, may be necessary. A set of postulates is offered to determine whether there is a causal relationship between low-level chemical exposures and symptoms using an environmental medical unit. — Environ Health Perspect 105(Suppl 2):445–453 (1997)

Key words: adaptation, chemical sensitivity, masking, multiple chemical sensitivity, sensitivity, sensitization, tolerance, addiction, habituation

Introduction

Clinical observations in North America (1–7) and Europe (8) point to an expanding group of patients who report sensitivities to extraordinarily low levels of environmental chemicals. This phenomenon, termed chemical sensitivity or multiple chemical sensitivity, appears to develop *de novo* in some individuals following acute or chronic exposure to a wide variety of environmental agents including various pesticides, solvents, drugs, and air contaminants in so-called sick buildings. Some practitioners have attributed a broad spectrum of chronic medical conditions involving any and every organ system to chemical sensitivity (Figure 1) (4).

Efforts to formulate a case definition for chemical sensitivity, to identify relevant biomarkers, and to explore a variety of mechanisms for the condition have escalated over the past decade. Several conflicting schools of thought have evolved with respect to underlying mechanisms, ranging from the purely psychological to the wholly physiological. In the midst of the tumult surrounding chemical sensitivity lies a profound but little-recognized scientific debate concerning the origins of disease. Some participants in this debate are challenging currently accepted notions concerning the causes for many chronic illnesses.

This paper attempts to clarify the nature of chemical sensitivity by describing a general mechanism that appears to underlie these cases; proposes a theory of disease based upon this general mechanism; and offers a set of testable postulates for corroborating or refuting this theory. Science is not about opinion or belief; it is about “guess and test,” that is, formulating hypotheses and then devising experiments to test them.

Terminology

Phenomenologically, chemical sensitivity appears to develop in two stages (3,4). First is the loss of tolerance (possibly but not necessarily due to sensitization) following acute or chronic exposure to various environmental agents such as pesticides, solvents, or contaminated air in a sick building. Second is the subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations (Figure 2). Although sensitivity to chemicals may be one of the consequences of this two-stage process, the term chemical sensitivity does not appropriately describe the process involved.

There are two principal reasons for this. First, although chemical sensitivity certainly sounds like an inconvenient problem to have, the words fail to convey the potentially disabling nature of the condition and its postulated origins in a toxic exposure. Some researchers balk at using the word toxic in this manner. However, numerous investigators from different geographic regions have published strikingly similar descriptions of individuals who report disabling illnesses after exposure to recognized environmental contaminants, albeit at levels not generally regarded as toxic (1,9–12). Yet, for these individuals, the exposure appears to have been toxic.

Paracelsus aptly opined that dose makes the poison. However, as our knowledge has grown, it has become evident that dose + host makes the poison (for example, pack-years of smoking plus α -1-antitrypsin deficiency). Similarly, in the case of chemical sensitivity, not everyone exposed in a sick building or to a chemical spill develops chronic illness. Thus, it may be concluded that individual susceptibility, whether physiological or psychological, must play a role in determining who gets sick. The term chemical sensitivity fails to convey this key observation that chemical exposures appear to initiate a process that results in chemical

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Abbreviations used: EMU, environmental medical unit; TILT, toxicant-induced loss of tolerance.

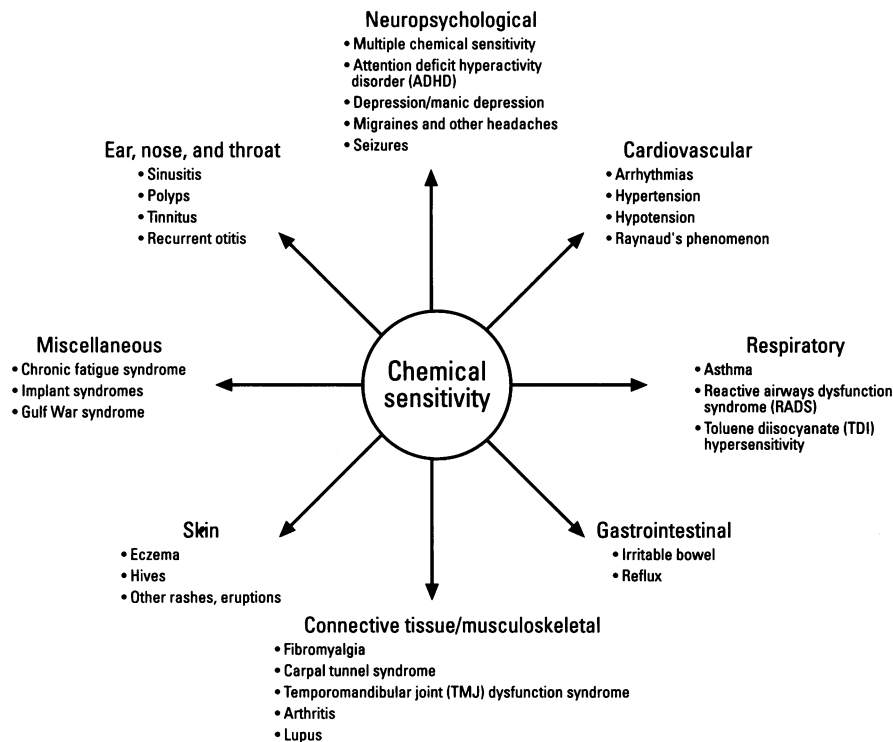


Figure 1. Some conditions that have been attributed to chemical sensitivity.

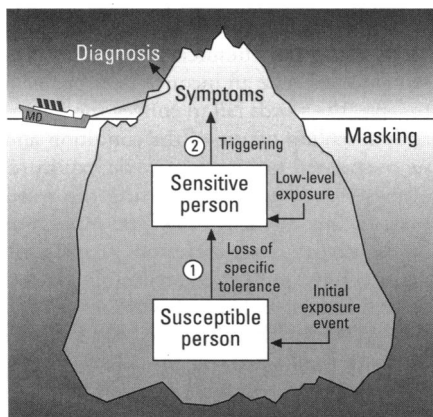


Figure 2. Phenomenology of chemical sensitivity. Chemical sensitivity appears to develop in two stages: Stage 1—loss of specific tolerance following acute or chronic exposure to various environmental agents such as pesticides, solvents, or contaminated air in a sick building; and Stage 2—subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations (e.g., traffic exhaust, fragrances, caffeine, alcohol). Physicians formulate a diagnosis based on symptoms reported to them by their patients. Because of masking, both physicians and patients may fail to observe that everyday low-level exposures are triggering symptoms. Sometimes even when such triggers are recognized, an initial exposure event that initiated loss of specific tolerance may go unnoticed or may not be linked by the physician or the patient to the patient's illness.

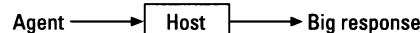
sensitivity. Conceivably, this phenomenon could represent a new type of toxicity.

The second problem with the term chemical sensitivity is that it suggests that those afflicted become intolerant of chemical exposures only when, in fact, caffeine, alcoholic beverages, various drugs, and foods reportedly trigger symptoms in these individuals once the process has been initiated (4,12–15). For the above reasons, chemical sensitivity is a misnomer for the process under discussion. An alternative term, toxicant-induced loss of tolerance (TILT), has been proposed (16). This term offers several advantages. First, it describes the process as it has been observed by clinicians and patients. Second, it allows for the possibility that various toxicants may initiate the process. Third, it does not limit the resulting intolerance to chemicals. Finally, it sharpens the focus of the current debate over chemical sensitivity by positing a theory of disease that can be subjected to objective testing.

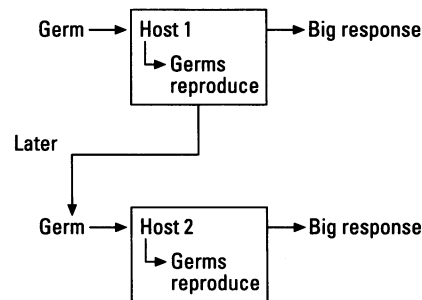
Historically, new theories of disease arose when physicians observed patterns of illness that did not fit accepted explanations for disease at that time, for example, the germ theory or the immune theory of disease. Similarly, many of the illnesses under discussion here do not conform to current

accepted explanations for disease or toxicity. Objections to the concept of chemical sensitivity have included concerns that: too many different chemicals have been said to cause chemical sensitivity; patients report too many symptoms involving any and every organ system; no known physiological mechanism explains chemical sensitivity; no biomarker has been identified for chemical sensitivity; and total avoidance of chemicals is impractical.

Theories of disease attempt to explain what is going on inside the patient (a "black box") before overt illness, as illustrated below:

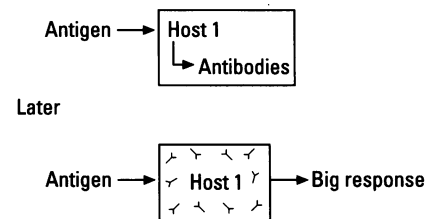


A theory of disease is a yet-to-be-established, general mechanism for a class or family of diseases. For the germ theory of disease, the boxes depicting the general mechanism of infection would look something like this:



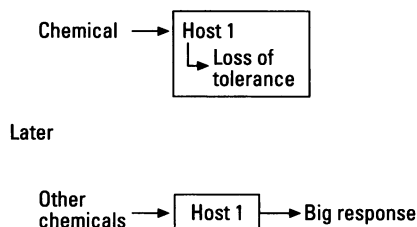
Note that: many different kinds of germs cause responses; there are many different responses involving any and every organ system (skin, respiratory, gastrointestinal); specific mechanisms vary greatly—for example, cholera versus AIDS versus shingles; there is no single biomarker—identification of specific germs took years; and prevention (avoidance, antiseptics, sanitation, use of gloves) preceded knowledge of specific mechanisms.

For the immune theory of disease, the boxes might look like this:



Here, just as for the germ theory of disease: many different kinds of antigens cause responses; there are many different responses involving any and every organ system (skin, respiratory, gastrointestinal); specific mechanisms vary greatly—for example, poison ivy versus allergic rhinitis versus serum sickness; there is no single biomarker—identification of specific antibodies took years; and prevention (avoidance, allergy shots) preceded knowledge of specific mechanisms.

For toxicant-induced loss of tolerance, the boxes might look like this:



For toxicant-induced loss of tolerance, as for the germ and immune theories of disease: many different kinds of chemicals may cause responses; there may be many different responses involving any and every organ system; specific mechanisms may vary greatly; it is conceivable that there is no single biomarker for response—identification of biomarkers may take years; and prevention (avoidance of initiators or triggers) may precede knowledge of specific mechanisms.

Although the concept loss of tolerance may sound vague, in fact it is not. What these individuals report is a loss of specific tolerance to particular chemicals, foods, and drugs. (16). Note that this theory does not exclude the possibility that toxicant-induced loss of tolerance could turn out to be a special kind of toxicity or a variation on the immune theory of disease just as allergy and delayed-type hypersensitivity are special cases that fall under the general classification of immunologic disorders. A consequence of viewing TILT as a theory of disease would be a shift in perspective from chemical sensitivity as a syndrome to chemical sensitivity, now TILT, as a class of disorders parallel to infectious diseases or immunologic diseases. Much effort has been devoted to developing a case definition for chemical sensitivity, with a singular lack of success. This lack of success would not be surprising if in fact TILT represented a new class or family of disorders. Certainly, it would not be feasible to

develop a single clinical case definition that would embrace all infectious or all immunologic diseases.

Theories of disease that withstand scientific scrutiny arise infrequently. The past century has witnessed the inculcation of the germ and immune theories of disease into medical practice. Equating toxicant-induced loss of tolerance to either one of these theories, both of which have been widely corroborated, would be premature and presumptuous. On the other hand, toxicant-induced loss of tolerance has certain earmarks of an emerging theory of disease, including the vituperative professional disputes that surround it (16).

Features of TILT Relevant for Its Testing

As described by many investigators, this phenomenon appears to involve a two-stage process. Because of ethical considerations, the first stage (initiation) is more difficult to model in humans than the second stage (triggering). Ultimately, epidemiologic studies and animal models may elucidate the first stage. Fortunately, the second stage readily lends itself to testing via direct human challenges, a potent form of scientific evidence. However, in the design of human challenge studies in this area, certain key clinical observations must be taken into account. First, the commonly reported biphasic, stimulatory-and-withdrawal-like pattern of the patients' symptoms, particularly those symptoms involving the central nervous system, must be understood to perform meaningful test challenges on these patients. Second, a related phenomenon called masking (to be described further) may hide responses to low-level chemical challenges and therefore may need to be minimized before testing. Controlling masking may be analogous to controlling background noise in studies on sound.

The following sections will discuss these clinical features, their incorporation in experimental designs, and how failure to do so might threaten research outcomes.

Stimulatory and Withdrawal Symptoms

Randolph first described the time course of the responses of these individuals to chemicals and foods (17). He reported striking parallels between their symptoms and those associated with alcohol and drug addiction. Randolph viewed the food and caffeine addictions his patients exhibited as the bottom rungs in a hierarchy of addiction, proceeding from foods and food and drug

combinations such as caffeine and alcohol on the lower rungs upward to nicotine and other naturally occurring and synthetically derived drugs (14).

Chemically sensitive patients resemble drug addicts in that members of both groups often report intense cravings and debilitating withdrawal symptoms. However, chemically sensitive patients' responses are not primarily to drugs. These individuals more commonly report addictions to caffeine or certain foods. While drug addicts manifest addicted behaviors (Latin *ad* "toward" + *dicare* "proclaim"), chemically sensitive patients respond as though they were ab-dicted (Latin *ab* "away from" + *dicare* "proclaim") and assiduously avoid the very substances addicted persons favor including alcohol, drugs and nicotine.

The stimulatory and withdrawal symptoms reported by chemically sensitive patients are frequently identical to those reported by normal persons exposed to much greater amounts of the same substances. For example, after drinking one cup of coffee, chemically sensitive patients may report feeling hyperactive, jittery, talkative, nervous, anxious, or experiencing paniclike symptoms (stimulatory phase). Hours to days later, they may report withdrawal symptoms such as fatigue, yawning, confusion, indecisiveness, irritability, depression, loss of motivation, blurred vision, headaches, flulike symptoms, hot or cold spells, or heaviness in their arms and legs (withdrawal phase). Similar symptoms occur during caffeine withdrawal among some low-to-moderate caffeine users in the general population (18). Large numbers of chemically sensitive patients and many Gulf War veterans with unexplained illnesses report that one drink of an alcoholic beverage causes inebriation and/or a severe hangover (12,15,19). These augmented responses suggest that those afflicted have lost their previous natural or native tolerance for such exposures.

Early in their illnesses, before eliminating caffeine from their diets, many chemically sensitive patients report having consumed chocolate, coffee, tea, or cola addictively, often in very large quantities (15). Some carried large containers of coffee or tea around wherever they went. Many report later stopping use of all caffeine and xanthines, generally on the advice of a friend or physician, and subsequently experiencing several days of intense withdrawal symptoms. Frequently they report that it was only after eliminating all xanthines from their diets that they were

able to discern the effects of consuming a single cup of coffee or a chocolate bar. Most report becoming aware of the unpleasant effects of caffeine only after a trial of partial or complete caffeine avoidance. In this regard, chemically sensitive patients resemble certain reformed smokers or alcoholics who after quitting their addictions report extreme sensitivity to minute amounts of the addicting agents. Terms like addiction, withdrawal, and detox pepper the vocabulary of chemically sensitive patients. One patient described the condition as being "like drug abuse without any of the fun." These parallels to addiction provide perspective: they may help explain why the mechanisms that underlie chemical sensitivity have been difficult to define and why biological markers have proven elusive.

In summary, drug addiction and TILT share a number of features in common. TILT also has features reminiscent of toxicity and allergy (Table 1). However, it is its resemblance to addiction that is perhaps most striking and that has escaped the attention of many physicians and researchers.

Masking

Suppose that TILT was a mechanism underlying certain cases of chronic fatigue, migraine, asthma, or depression. It might be reasonable to wonder, then, why patients experiencing these symptoms do not also report chemical intolerances. In fact, some but not all patients do report them (21,22). Many chemically sensitive patients with these same diagnoses report that it was not until they accidentally or intentionally avoided a sufficient number of their problem incitants that they noticed feeling better. Then, when they encountered one of those incitants, robust symptoms occurred. As they repeated this iterative process of avoidance and reexposure, they noticed that particular symptoms occurred with particular exposures. Most indicate that had they not avoided many chemicals and foods simultaneously, or unmasked themselves, they might not have determined what was making them sick.

Masking and unmasking are colorful lay terms for which there is no scientific equivalent. Nevertheless, investigators' abilities to understand masking and unmasking and manipulate these variables knowledgeably may determine the success of studies in this area. When chemically sensitive patients follow a diet free of their problem foods and live in a relatively chemical-free home in the hills of central Texas where there are no major agricultural or industrial

Table 1. Features of toxicant-induced loss of tolerance compared with features of addiction, allergy, and toxicity.

Feature	Toxicant-induced loss of tolerance ^a	Addiction ^a	Allergy ^a	Toxicity ^a
Chemical/drug intolerance	+	+	+	+
Ambient air incitants	+		+	+
Food intolerance	+		+	
Alcohol intolerance	+	+		
Caffeine intolerance	+	+		
Withdrawal symptoms	+	+		
Craving, bingeing	+	+		
Sensitization	+		+	
Induction by chemicals	+		+	+
Induction by biologicals			+	
Multisystem symptoms	+	+	+	+
Frequent CNS symptomatology	+	+		+
Well-defined mechanism(s)			+	+
Genetic susceptibility	+	+	+	+
Dose-response relationship	+		+	+

^aCategories are not pure and may overlap in a given host, e.g., haptentation of a chemical toxin may initiate an immunologic response; brain and liver toxicity may accompany alcohol addiction. ^bLow molecular weight chemicals may combine with tissue proteins producing haptens that evoke immune responses. ^cDose response does occur for allergens. With the first sensitizing exposure in a susceptible individual, there is a dose-response relationship; with subsequent exposures, the sensitized person also responds in proportion to dose but at a much lower dose level (20). The same kind of dose-response relationship may hold true for TILT but this has not been tested. Chemically sensitive individuals generally report increasingly severe symptoms the longer they remain in exposure situations, an observation that suggests a dose-response relationship.

operations or air contaminants, they say they are in an unmasked state. Under these circumstances they claim that if a diesel truck drove by they could identify specific symptoms due to the diesel exhaust, for example, irritability, headache, or nausea.

On the other hand, the patients report that when they travel to a large city like Houston or New York City, stay in a hotel room, and eat in restaurants, they become masked. In the presence of many concurrent exposures (exhaust, fragrances, volatiles offgassing from building interiors, various foods) in New York City many report feeling chronically ill, as if they had flu. If a diesel truck drove by under these circumstances, most report they would not be able to attribute any particular symptoms to the exhaust because of background noise from overlapping symptoms occurring as a consequence of overlapping or successive exposures. In theory, such background noise or masking hides the effects of individual exposures—responses are blurred.

Masking appears to involve at least three interrelated components, any of which may interfere with the outcome of low-level chemical challenges in these individuals: acclimatization, apposition, and addiction. In real life, these three components probably operate concurrently, although here they are considered individually.

There is some notation that can be used to help depict these components. In the addiction literature, responses to addictive

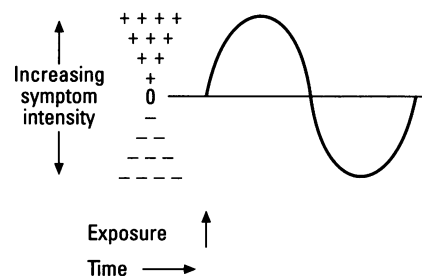


Figure 3. Graphic representation of symptom progression following exposure to a single substance in a person sensitive to that substance (e.g., caffeine, a solvent, alcohol, nicotine). The portion of the biphasic curve above the line represents symptoms with onset of exposure (stimulatory symptoms) and the portion of the curve below the line represents symptoms with offset of exposure (withdrawal symptoms). Amplitude is proportional to symptom severity. The length of the curve (duration of symptoms) may range from minutes to days.

drugs are often illustrated graphically using a biphasic curve or sine wave (Figure 3). The portion of the sine wave above the horizontal axis represents symptoms with onset of exposure, often called stimulatory symptoms; the portion below the horizontal axis represents symptoms with offset or cessation of exposure, often referred to as withdrawal symptoms. The height or amplitude of the sine wave in either direction is proportional to the severity of the response. For persons not sensitive to a particular substance, the curve would be a

flat line with zero amplitude in either direction. The length of the biphasic curve represents the duration of symptoms following an exposure, reportedly ranging from minutes up to several days depending upon the exposure and the individual. Of course, the particular nature of the symptoms vary from one sensitive subject to the next and from substance to substance.

Suppose researchers wished to test a putatively sensitive subject by exposing him to a low concentration of xylene. Xylene is a common indoor air contaminant and a component of Molhave's mixture (23) that has been used in human inhalation challenge studies. How would the researchers ensure that their subject was unmasked (at true baseline) before challenge? The following components of masking would need to be considered and controlled:

Acclimatization. For most of the population, with continuous or repeated exposure to many environmental stressors, adaptation occurs. That is, symptoms diminish as exposure continues. Chemically sensitive patients' symptoms also decrease with continuing exposure; however, when exposure ceases, these individuals often report marked withdrawal symptoms. Thus, what they describe is more akin to habituation than to adaptation. Suppose further that the subject who is challenged with xylene works in a sick building where he is routinely exposed to low levels of xylene on a regular basis. Administering a test exposure of xylene below the odor threshold (0.62 ppm) (24) may produce little or no effect on the subject if he has been working in that same building during the preceding week (Figure 4). On the other hand, if he avoided the building and all other sources of xylene for 4 to 7 days before testing, a more robust response to the xylene challenge might be anticipated.

Thus, a sensitive subject's response to a challenge may range widely in intensity, from none to maximal, depending on how recently that person has been exposed to the test substance or a chemically related substance. If insufficient time has elapsed, for example, less than 4 days, the challenge may yield a false negative response as a result of habituation. If too much time has elapsed, for example, weeks or months, sensitivity may have waned.

Apposition. Suppose next that the research subject is sensitive to multiple substances. On the day he is scheduled for challenge testing, he gets up in the morning, uses some scented soap or hair spray, cooks breakfast on a gas stove, and drives

his car through heavy traffic to reach the laboratory. Inside the laboratory building he rides an elevator where he is exposed to people wearing various colognes. If he were sensitive to several of these exposures, his responses might overlap in time. Such responses reportedly can last for hours or days. If this is true, they could persist during a placebo challenge, resulting in a false positive response. Thus, apposition or juxtaposition of the effects of closely timed exposures is a second component of masking that must be controlled prior to and during challenge studies (Figure 5).

Addiction. Many of the symptoms reported by chemically sensitive patients mirror those commonly associated with addiction. Addiction may be a component of masking. Addicted individuals consciously or subconsciously time their next "hit" so as to forestall withdrawal symptoms (Figure 6), a phenomenon that occurs in alcohol, tobacco, and caffeine addictions. However, addiction to foods also is reported among chemically sensitive patients. Randolph described wheat, eggs, milk, and corn as the most common addic-tants in his patients (14,17). Frequently

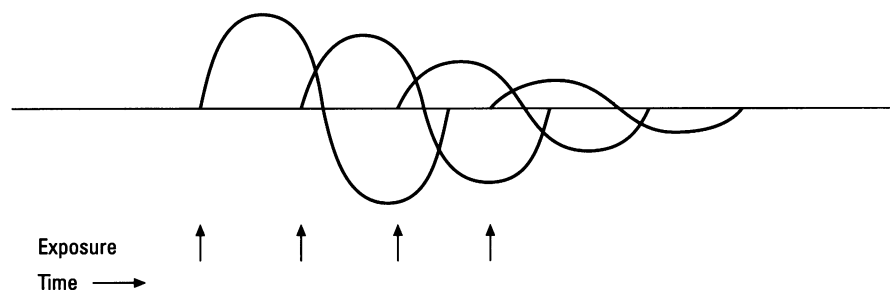


Figure 4. Graphic representation of acclimatization. Symptom severity decreases with repeated closely timed exposures (inhalant or ingestant) to the same substance. Acclimatization is not equivalent to adaptation, since patients report withdrawal symptoms after exposures cease; conceptually, acclimatization more closely resembles habituation in this case.

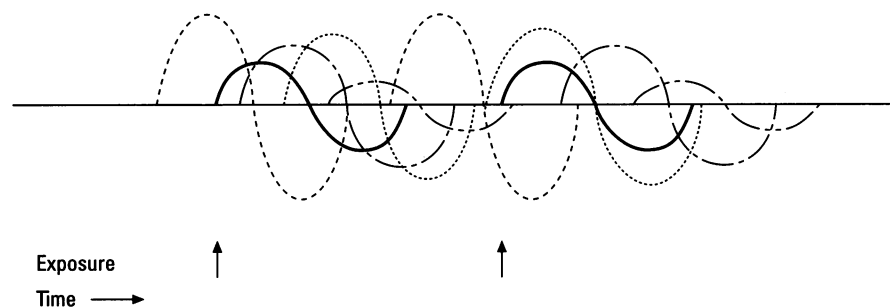


Figure 5. Graphic representation of apposition. If an individual is sensitive to many different substances, the effects of everyday exposures to chemicals, foods, or drugs may overlap in time. This apposition of effects might lead to an individual who feels ill most of the time; however, neither the individual nor his physician notices the effect of any single exposure. Apposition tends to mask the effect of interest (solid lines) in much the same way that background noise masks a sound of interest.

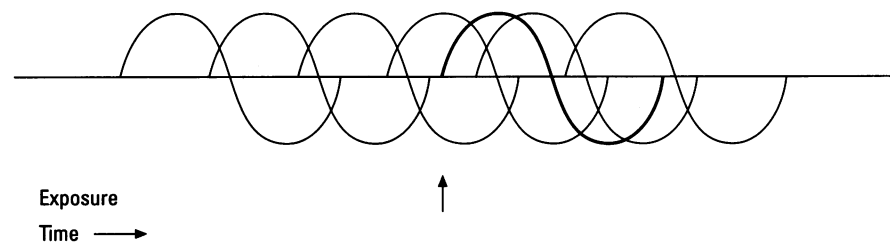


Figure 6. Graphic representation of addiction. A sensitive person who is addicted to caffeine, alcohol, nicotine, or another substance may deliberately take that substance at frequent, carefully spaced intervals to avoid unpleasant withdrawal symptoms. Such exposures may also mask the effect of interest (e.g., a challenge test using xylene).

these individuals report intense cravings and consume astounding quantities of foods, for example, a pound of chocolate, several bags of popcorn, a dozen doughnuts, or 30 cups of coffee in one day. Patients most often report this kind of addictive consumption in the early stages of their illness, before they practiced avoiding problem exposures.

Foods may contain bioactive constituents such as tyramine, monosodium glutamate, and opiates (13). Persons who routinely use tobacco, caffeine, alcohol, or foods containing bioactive substances may need to avoid these substances before testing because the pharmacologic effects of these agents could override or mask the effect of an experimental challenge. Failure to eliminate adductants before testing could result either in false positive challenges due to lingering symptoms from an adductant used in the hours or days preceding a placebo challenge or in false negative challenges due to masking by an adductant.

Testing the TILT Theory

After the germ theory of disease was introduced in the late 1800s, many overly enthusiastic investigators who were careless in their bacteriological techniques announced they had discovered causative agents for tuberculosis, yellow fever, and other diseases. These pronouncements and subsequent retractions became so frequent that in 1884 the President of the New York Academy of Medicine lamented that a bacteriomania had swept over the medical profession (25). To prevent future such pseudodiscoveries, Robert Koch, who identified the organisms responsible for tuberculosis, anthrax, and cholera, proposed a set of rules for etiological verification. His postulates required that: the microbe must present in every case of the disease; it must be isolatable in pure culture; inoculating a healthy animal with the culture must reproduce the disease; and the microbe must be recoverable from the inoculated animal and be able to be grown again.

Just as bacteriomania engulfed the medical profession in the 1880s, chemomania is poised to engulf it now. Chemical sensitivity is in need of a set of postulates to ensure that future causal determinations are scientifically based. Below is a set of postulates that, if met, would confirm (and if not met, refute) that a person's symptoms were caused by a particular substance:

- When a subject simultaneously avoids all chemical, food and drug incitants, remission of symptoms occurs (unmasking).

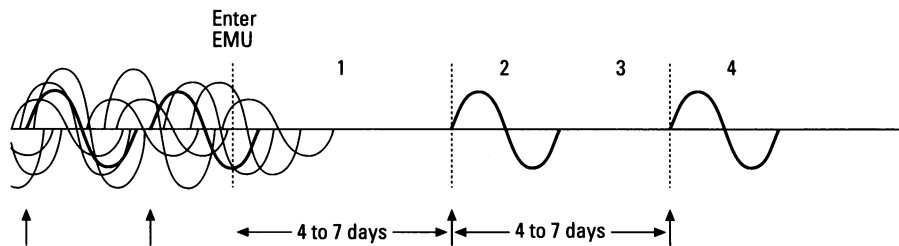


Figure 7. Graphic representation depicting the testing of the toxicant-induced loss of tolerance postulates using an environmental medical unit. In the left-hand portion of the figure, a chemically sensitive individual is experiencing symptoms in response to multiple exposures (chemicals, foods, drugs) before entering the environmental medical unit. Effects overlap in time. The effect of any particular exposure cannot be distinguished from the effects of other exposures, and the person's symptoms may appear to wax and wane unpredictably over time. Postulate 1—When all chemical, food, and drug incitants are avoided concurrently, remission of symptoms occurs. Anecdotally, patients report going through withdrawal or detox for the first several days during which they experience symptoms such as increased irritability, headaches, and depression. After 4 to 7 days, most report feeling well and theoretically are at a clean baseline. Postulate 2—A specific constellation of symptoms occurs with reintroduction of an incitant. Postulate 3—Symptoms resolve when the incitant is again avoided. Postulate 4—Reexposure to the same incitant within an appropriate window of time (estimated to be about 4–7 days) produces the same symptoms. For research purposes, challenges should be conducted in a double-blind, placebo-controlled manner.

- A specific constellation of symptoms occurs with reintroduction of a particular incitant.
- Symptoms resolve when the incitant is again avoided.
- With reexposure to the same incitant, the same constellation of symptoms reoccurs, provided that the challenge is conducted within an appropriate window of time. Clinical observations suggest that an ideal window is 4 to 7 days after the last exposure to the test incitant.

To apply these postulates (illustrated in Figure 7), the timing of exposures and the degree of masking should be rigorously

controlled. To accomplish this, a hospital-based clinical research facility, an EMU, is needed to isolate subjects from background exposures (Figure 8) (4,5,15,16,26). The EMU would be constructed, furnished, and operated to minimize exposure to airborne chemicals. For example, no disinfectants, perfumes, or pesticides would be allowed in the unit. Ventilation would maximize fresh outside air and provide optimal particulate and gas filtration. Patients would eat chemically less-contaminated foods and water, testing one food per meal to determine the effects of specific foods. If symptoms persisted despite this

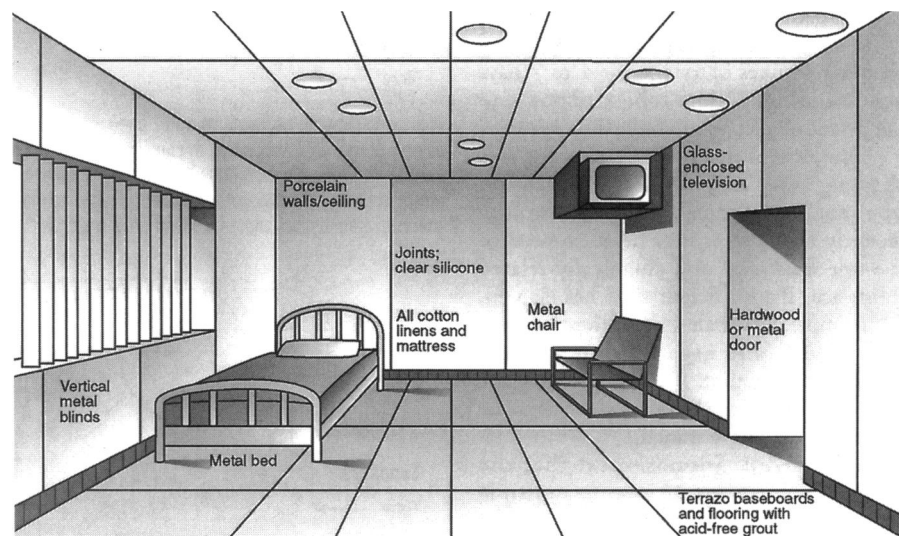


Figure 8. Preliminary design sketch of a patient room in an environmental medical unit. Note use of the nonout-gassing construction materials and furnishings and point source control (ventilated television enclosure).

approach, fasting for a few days would be attempted before reintroducing single foods.

The rationale for housing subjects in an environmentally controlled facility for several days before challenges is 2-fold: to prevent extraneous exposure of patients to inhalants or ingestants so responses to them are not misinterpreted as positive responses when placebo challenges are administered (false positives), and to minimize masking that might blunt or eliminate responses to active challenges (false negatives).

Although the terms exposure chamber and environmental medical unit appear similar, conceptually they differ in important ways with regard to patient safety and control of interfering exposures.

By definition, an EMU is in a hospital where patients can remain 24 hr a day in a clean environment for up to several weeks. Like an intensive care unit or coronary care unit, the EMU would be a specialized, dedicated hospital facility. The EMU must be in a hospital to accommodate very sick patients; exposure chambers do not offer comparable levels of care. Because chemical challenges may precipitate bronchoconstriction, mental confusion, severe headaches, depression, and other disabling symptoms, these patients should not be tested in an exposure chamber on an outpatient basis.

Conventional exposure chambers do not reduce background chemical exposures for extended periods (up to several weeks) so the effects of a particular challenge in a patient can be assessed accurately. This is the central limitation of exposure chambers and the reason they should not be used to rule in or rule out chemical sensitivity. If subjects are not kept in a clean environment for several days before and during challenges, false positive responses may occur because of interfering exposures and false negative responses may occur because of masking. In contrast to an exposure chamber, an EMU would minimize interfering exposures before and during challenges, thus maximizing the reliability and reproducibility of test responses.

Availability of an EMU would allow physicians to refer a wide variety of cases in which environmental sensitivities were suspected to the unit for definitive evaluation. There physicians could observe first-hand whether a patient's symptoms improved after several days on a special diet in a clean environment. If improvement occurred, single chemicals at concentrations encountered in normal daily living as well as single foods could be reintroduced one at a time while the effects of each introduction were

observed. Thus, the EMU would be a tool to determine in the most direct and definitive manner possible whether chemical sensitivities exist. Studying patients with complicated conditions like chronic fatigue syndrome or Gulf War syndrome in a conventional exposure chamber would not provide the same information, since chambers allow only short-term residence, do not control the entire range of background contaminants, and provide inadequate separation from background exposures prior to challenges.

An analogy may help illustrate the importance of controlling exposures for extended periods before challenge. If one wished to determine whether a coffee drinker's headaches were due to caffeine, it would not be adequate simply to give the person a cup of coffee and ask him how he felt. It is obvious that the individual would have to stop using caffeine for a period before a meaningful test of caffeine sensitivity could be performed. In this instance, a false negative challenge likely would be the result of failure to avoid coffee before challenge. Similarly, placing a putatively sensitive person in a conventional exposure chamber and exposing him to a low concentration of a chemical might not produce any noticeable effect. On the other hand, if this same person remained in a clean environment such as an EMU for a few days before being tested and his condition improved, one could then perform meaningful challenges.

Placing patients in an EMU would simultaneously control all three components of masking: stopping all exposures several days before challenge testing and spacing test exposures 4 to 7 days apart would preclude acclimatization or habituation; eliminating background chemical noise and allowing the effects of each challenge to subside before introducing the next one would control apposition; and excluding drugs, alcohol, nicotine, and caffeine and spacing introduction of individual foods 4 to 7 days apart would interrupt any addiction. Individual sensitivity could then be evaluated in the EMU following the postulates in Figure 7 for etiological verification.

For research purposes, challenges must be performed in a double-blind, placebo-controlled manner. Patients with chronic fatigue syndrome, migraine headaches, seizures, depression, asthma, or unexplained illnesses such as Persian Gulf illness could also be tested for sensitivities in an EMU using these postulates. Thus, the EMU could be used to determine whether

particular patients with these diagnoses had a masked form of this illness.

What evidence is there that unmasking patients in an EMU and conducting challenges within a 4- to 7-day window of time is either useful or necessary? Thousands of credible patients and dozens of physicians have attempted this approach. They report that patients' symptoms resolve within a few days after they enter such a facility and that robust symptoms occur when challenges are conducted after several days of avoidance. Other evidence corroborates these observations: Withdrawal symptoms of several days' to a week's duration are known to occur in some persons following cessation of exposure to nitroglycerine (dynamite workers' headaches) (27), caffeine (18,28), nicotine, and alcohol. Note that these substances are chemically unrelated. In individuals chronically exposed to xylene (29) or ozone (30), reexposure after several days' avoidance results in robust symptoms. Foods may require one to several days to navigate the digestive tract before they are eliminated. Taken together, these observations suggest that individuals with sensitivities to multiple incitants might experience effects that linger as long as several days following initial avoidance. Thus, it may be argued that patients should be removed from their entire background of food and chemical exposures for 4 to 7 days before challenges, as Randolph first proposed (14,17).

While it is conceivable that synergistic or additive chemical combinations may be necessary to reproduce certain symptoms, this is a limitation of any form of challenge testing. Wherever possible within the bounds of safety and feasibility, chemical combinations believed to precipitate the most robust and measurable responses should be explored. However, 40 years of clinical observations, although anecdotal, suggest that single test substances may suffice for most sensitive subjects. Confirmation or refutation of these claims seems a logical first step that should precede testing of complex mixtures. Finally, because isolating patients in a hospital environment like the EMU may have unanticipated psychological consequences, early studies in this area should examine the responses of control subjects in the same environment.

Conclusion

Good pathological and physiological theories provide "a unified, clear, and entirely intelligible meaning for a whole series of anatomical and clinical facts, and for the relevant

experiences and discoveries of reliable observers..." (31). Theories and experiments that overlook salient observations or do not control experimental conditions adequately may lead to erroneous conclusions. During the late 19th century, researchers collected sputum from patients with tuberculosis but were unsuccessful in culturing any organism. Some concluded that tuberculosis was not an infectious disease. These early investigators did not know that the tuberculin bacillus was fastidious and would grow out only after many weeks on a specialized culture medium. Correspondingly, scientists' abilities to observe and understand chemical sensitivity may depend on optimizing experimental conditions, that is, appropriate timing of challenges and use of an EMU for unmasking patients. To date, studies in this area have failed to unmask patients before challenge. When false positive and false negative responses occurred, investigators concluded that chemical sensitivity was psychogenic in origin (32,33).

In summary, features of TILT overlap those of allergy, addiction, and classical toxicity, yet TILT may be distinct from each of these. TILT appears to involve a two-step process (resembling allergic sensitization) in which persons lose specific tolerance (resembling addiction) for a wide range of common substances following a chemical exposure event (resembling toxicity). Just as the germ theory describes a class of diseases sharing the general mechanism of infection, the TILT theory of disease posits a class of chemically induced disorders characterized by loss of tolerance to chemicals, foods, drugs, and food and drug combinations. In the same way that fever is a symptom commonly associated with infectious diseases, chemical sensitivity may be a symptom associated with the TILT family of diseases. Although clinical case definitions have been developed that describe particular infectious diseases, no clinical case definition can be applied to the entire class of infectious diseases. The

same may be true for TILT disorders. The fact that this phenomenon does not fit already accepted mechanisms for disease is often offered as evidence that the condition does not exist. However, the same criticism would have applied to the germ and immune theories of disease when they first were proposed. What is plausible depends on the biological knowledge of the time (34).

Looking to the future, carefully conducted epidemiological studies and animal models likely will play important roles in characterizing the initiation stage of TILT during which tolerance is lost. In the meantime, rigorous testing of the second stage of TILT, that is, the triggering of symptoms by tiny doses of chemicals, foods, drugs, caffeine, or alcohol, is needed if progress in this area is to occur. Adopting a set of relevant testable hypotheses for etiological verification will ensure the credibility of those endeavors.

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